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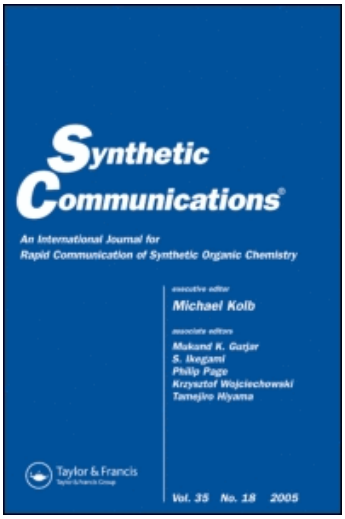

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ONE-POT ALKOXYMERCURIATION-BROMODEMERCURIATION: A VERSATILE ACCESS TO 3-ALKOXY-2-BROMOPROPANOIC ESTERS

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Abstract: A convenient one-pot methodology for the preparation of 3-alkoxy-2-bromopropanoic esters from alkyl acrylates is described. The use of stoichiometric amounts of alkyl acrylate, alcohol and mercury trifluoroacetate in THF makes this procedure versatile and attractive to achieve building blocks for the synthesis of targeted contrast agents for Magnetic Resonance Imaging.

3-Alkoxy-2-halopropanoic esters are useful intermediates for the preparation of ligands, which after complexation with a paramagnetic metal ion (e. g. Gd(III), Fe(III), Mn(II)...) can be used as contrast agents for Magnetic Resonance Imaging (MRI).[1] These intermediates allow the synthesis of linear (DTPA-like[2]) and cyclic (DOTA-like[3]) ligands which carry on the acetic residues substituents specific for targetting of selected organs and tissues.[4]

Some 3-alkoxy-2-halopropanoic esters have been synthesized by Mannich addition of alcohols to 2-halopropenoic esters.[5] Handling of such intermediates is not always easy due to concurrent polymerization[6] and therefore in situ dehydrohalogenation of 2,3-dihalopropanoic esters immediately followed by reaction with the alcohol has

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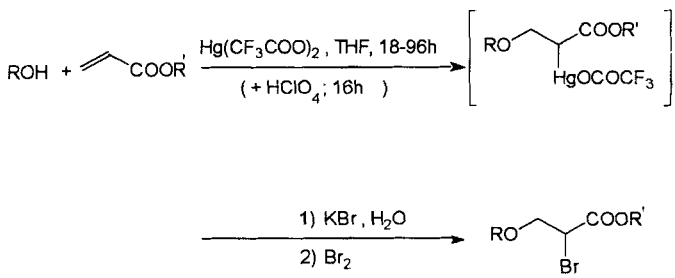
sometimes been preferred.[7] However, with this synthetic approach, in our laboratories good yields have been obtained only when the alcohol is used as the solvent. Moreover a major drawback for reactions via haloacrylic intermediates is the concurrent transesterification which occurs to a large extent when the nucleophilic alcohol is different from the alcohol contained in the ester residue.[5] Although alkoxymercuriation-demercuriation of acrylic esters has also been used for the preparation of 3-alkoxy-2-halopropanoic esters, this route has always been limited to reactions in which the alcohol is used in very large excess (solvent).[8]

Since for our purposes we ought to use almost stoichiometric amounts of solid and sometimes expensive alcohols, it was important to develop a versatile procedure. Alkoxymercuriation of alkyl acrylates with $Hg(CF_3COO)_2$ in THF followed, after $CF_3COO \rightarrow Br$ exchange on the mercuro-derivative, by demercuriation with bromine afforded 3-alkoxy-2-bromopropanoic esters in 33-70% yields (Scheme) without isolation of any intermediate. In agreement with previous reports[9] we observed that mercury

Scheme



R = C_6H_{11}, $C_6H_{11}CH_2$, C_6H_5, 4-(X)-$C_6H_4CH_2$ [X = H, NO_2, Cl,..]

R' =Me, *t*-Bu

trifluoroacetate performs much better than the corresponding acetate according to the decreased nucleophilicity of the anion.

This one-pot methodology proved quite efficient irrespective of the alcohol used: primary and secondary alcohols, phenols and benzyl alcohols were successfully employed (Table). Benzyl alcohols with different substituents in the para position of the aromatic ring have been studied. All substrates (Entries 4 - 7, 17) gave the expected product while 4-ethoxybenzyl alcohol (Entry 8) afforded *t*-butyl 2-bromo-3-[(3-bromo-4-ethoxyphenyl)methoxy]propionate as the main product due to bromination of the highly activated aromatic ring in the demercuriation step.

Some of the reactions were performed using percloric acid (0.02 equiv) as a catalyst[10] (Table). This led to a noticeable decrease in the reaction time required for the alkoxymercuriation step without improving the final yields.

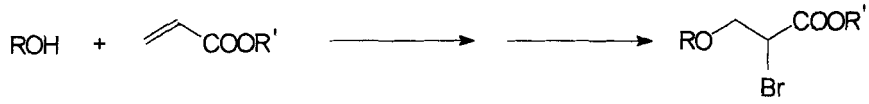
When *t*-butyl instead of methyl esters were used slightly lower yields of 3-alkoxy-2-bromopropanoic esters were obtained. (Table: entries 5 and 6, entries 13 and 14).

Experimental

Organic and inorganic reagents were purchased from E. Merck, Darmstadt, Germany and Aldrich, Milwakee, USA. Mercury trifluoroacetate was freshly prepared according to the procedure of Brown and Rei.[11] ^{1}H- and ^{13}C-NMR spectra were recorded on a *Bruker AC 200* spectrometer.

General procedure: A 1M solution of $Hg(CF_3COO)_2$ (1 equivalent) in THF was added dropwise in 1h to a solution of acrylic ester (2M, 1 equivalent) and the appropriate alcohol (2M, 1 equivalent) [and 72% $HClO_4$ (0.04 M, 0.02 equivalent) when required (see Table)] in THF under inert atmosphere maintaining the reaction temperature at 0°C. The resulting solution was stirred at 20°C (see Table for reaction

Table



Entry	R	R'	Time (h)[a]	Yield (%)[b]
1[c]	cyclohexyl	Me	24	42
2[c]	cyclohexylmethyl	Me	18	45
3[c]	phenyl	Me	72	33
4[c]	benzyl	Me	72	55
5[c]	4-NO_2-benzyl	Me	30	58
6[c]	4-NO_2-benzyl	*t*-Bu	96	33
7[c]	4-Cl-benzyl	Me	72	40
8[c]	4-EtO-benzyl	*t*-Bu	--	0[d]
9[e]	cyclohexyl	*t*-Bu	16	52
10[e]	cyclohexylmethyl	Me	16	70
11[e]	cyclohexylmethyl	*t*-Bu	16	45
12[e]	phenyl	Me	16	34
13[e]	benzyl	Me	16	56
14[e]	benzyl	*t*-Bu	16	37[f]
15[e]	4-NO_2-benzyl	*t*-Bu	16	40
16[e]	4-Cl-benzyl	Me	16	57
17[e]	4-CF_3-benzyl	Me	16	41

[a] For the mercuriation step.
[b] Yield in isolated product.
[c] Uncatalyzed reaction
[d] After 72h *t*-butyl 2-bromo-3-[(3-bromo-4-ethoxyphenyl)methoxy]propanoate is isolated in 35% yield.
[e] With the addition of 72% aq. $HClO_4$ (0.02 equiv.).
[f] HPLC yield

time). A 2.5M solution of KBr (1 equivalent) in H_2O was added dropwise to the reaction solution in 1h maintaining the reaction temperature at 0 to 5°C. After 1h at 25°C the solution was cooled at 0°C and Br_2 (1 equivalent) was added dropwise. The reaction was over in less then 1h. The solvent was evaporated, the residue was taken up in $CHCl_3$ and the inorganic salts were filtered. The solution was washed three times with H_2O, dried (Na_2SO_4) and concentrated to dryness. The reaction crude was purified by column chromatography [silica gel; *n*-hexane : EtOAc 15 : 85 (v/v)] to afford the 3-alkoxy-2-bromopropanoic ester as an oil.

Methyl 2-bromo-3-(cyclohexyloxy)propanoate: colorless oil; ^{1}H-NMR ($CDCl_3$): δ 1.12 - 1.25 (m, 5H), 1.44 - 1.47 (m, 1H), 1.64 - 1.82 (m, 4H), 3.23 - 3.30 (m, 1H), 3.67 - 3.75 (m, 4H), 3.84 - 3.93 (m, 1H), 4.22 (dd, 1H); ^{13}C-NMR ($CDCl_3$): δ 23.7; 25.5; 32.0; 41.0; 52.8; 68.9; 78.4; 169.1.

Methyl 2-bromo-3-(cyclohexylmethoxy)propanoate: colorless oil; ^{1}H-NMR ($CDCl_3$): δ 0.80 - 0.96 (m, 2H), 1.09 - 1.32 (m, 3H), 1.46 - 1.73 (m, 6H), 3.30 (dd, 2H), 3.69 - 3.79 (m, 4H), 3.9 (dd, 1H), 4.31 (dd, 1H); ^{13}C-NMR ($CDCl_3$): δ 25.6, 26.4, 29.3, 37.7, 41.6, 52.8, 71.7, 77.4, 170.0.

***t*-Butyl 2-bromo-3-(cyclohexylmethoxy)propanoate:** colorless oil; ^{1}H-NMR ($CDCl_3$): δ 0.84 - 0.96 (m, 2H), 1.06 - 1.22 (m, 4H), 1.44 (s, 9H), 1.51 - 1.71 (m, 5H), 3.23 (dd, 2H), 3.63 (dd, 1H), 3.81 (dd, 1H), 4.13 (dd, 1H); ^{13}C-NMR ($CDCl_3$): δ 25.7, 26.5, 27.6, 29.7, 37.8, 43.5, 71.7, 77.3, 72.2, 167.4.

Methyl 2-bromo-3-phenoxypropanoate: colorless oil; ^{1}H-NMR ($CDCl_3$): δ 3.76 - 3.89 (m, 4H), 3.87 (dd, 1H), 4.27 (dd, 1H), 7.34 (s, 5H); ^{13}C-NMR ($CDCl_3$): δ 41.7, 53.0, 71.3, 115.7, 121.4, 130.1, 155.1.

Methyl 2-bromo-3-(phenylmethoxy)propanoate: colorless oil; ^{1}H-NMR ($CDCl_3$): δ 3.80 - 3.83 (m, 4H), 3.98 (dd, 1H), 4.35 (dd, 1H), 4.59 (s, 2H), 7.33 (s, 5H); ^{13}C-NMR ($CDCl_3$): δ 41.7, 53.0, 70.7, 73.4, 127.8, 128.4, 137.3, 168.8.

***t*-Butyl 2-bromo-3-(phenylmethoxy)propanoate**: colorless oil; ^{1}H-NMR ($CDCl_3$): δ 1.49 (s, 9H), 3.76 (dd, 1H), 3.94 (dd, 1H), 4.26 (dd, 1H), 4.59 (s, 2H), 7.34 (s, 5H); ^{13}C-NMR ($CDCl_3$): δ 27.7, 43.6, 70.1, 73.4, 82.5, 127.7, 128.4, 137.4, 167.4.

Methyl 2-bromo-3-[(4-nitrophenyl)methoxy]propanoate: colorless oil; ^{1}H-NMR ($CDCl_3$): δ 3.76 - 3.87 (m, 4H), 4.00 (t, 1H), 4.38 (dd, 1H), 4.67 (s, 2H), 7.43 (s, 1H), 7.48 (s, 1H), 8.14 (s, 1H), 8.17 (s, 1H); ^{13}C-NMR ($CDCl_3$): δ 41.3, 53.1, 71.3, 72.1, 123.5, 127.7, 144.9, 147.4, 168.6.

***t*-Butyl 2-bromo-3-[(4-nitrophenyl)methoxy]propanoate**: colorless oil; ^{1}H-NMR ($CDCl_3$): δ 1.49 (s, 9H), 3.83 (dd, 1H), 3.97 (dd, 1H), 4.28 (dd, 1H), 4.69 (s, 2H), 7.47 (s, 1H), 7.52 (s, 1H), 8.19 (s, 1H), 8.24 (s, 1H); ^{13}C-NMR ($CDCl_3$): δ 27.6, 43.2, 71.4, 72.0, 82.7, 123.5, 127.6, 145.1, 147.3, 167.1.

Methyl 2-bromo-3-[(4-chlorophenyl)methoxy]propanoate: colorless oil; ^{1}H-NMR ($CDCl_3$): δ 3.77 - 3.87 (m, 4H), 3.98 (dd, 1H), 4.38 (dd, 1H), 4.59 (s, 2H), 7.21 - 7.33 (m, 4H); ^{13}C-NMR ($CDCl_3$): δ 41.5, 53.0, 70.8, 72.6, 128.5 - 128.9, 133.6, 135.8, 168.8.

***t*-Butyl 2-bromo-3-[(4-trifluoromethylphenyl)methoxy]propanoate**: colorless oil; ^{1}H-NMR ($CDCl_3$): δ 3.82 (dd, 4H), 3.98 (t, 1H), 4.38 (dd, 1H), 4.63 (s, 2H), 7.41 (s, 1H), 7.45 (s, 1H), 7.58 (s, 1H), 7.62 (s, 1H); ^{13}C-NMR: δ 41.4, 53.0, 71.0, 72.5, 125.3, 127.5, 141.4, 168.7.

Methyl 2-bromo-3-[(3-bromo-4-ethoxyphenyl)methoxy]propanoate: colorless oil; ^{1}H-NMR ($CDCl_3$): δ 1,39 - 1,42 (m, 3H), 1.46 (s, 9H), 3.75 (dd, 1H), 3.91 (dd, 1H), 3.99 (dd, 2H), 4,07 (dd, 1H), 4.44 (s, 2H), 6.81 (d, 1H), 7.15 (dd, 1H), 7.47 (d, 2H); ^{13}C-NMR ($CDCl_3$): δ 14.6, 27.7, 43.5, 64.7, 70.8, 72.3, 82.6, 112.9, 127.9, 130.9, 132.8, 154.9, 167.3.

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